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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/444,790	05/19/1995	MANFRED BROCKHAUS	9189	5612

37500 7590 05/25/2011

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LAW DEPARTMENT
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EXAMINER	
HOWARD, ZACHARY C	
ART UNIT	PAPER NUMBER
1646	
MAIL DATE	DELIVERY MODE
05/25/2011	PAPER

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RECORD OF ORAL HEARING

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte MANFRED BROCKHAUS

Appeal No. 2009-014889
Application No. 08/444790
Technology Center 1600

Oral Hearing Held: November 2, 2010

Before CAROL SPIEGEL, DEMETRA MILLS and LORA GREEEN, *Administrative Patent Judges.*

APPEARANCES:

ON BEHALF OF THE APPELLANT:

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The above-entitled matter came on for hearing on Tuesday, November 2, 2010, commencing at 9:03 a.m., at the U.S. Patent and Trademark Office, 600 Dulany Street, Alexandria, Virginia, before Paula Lowery, Notary Public.

PROCEEDINGS

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THE CLERK: Good morning. Calendar Number 1, Appeal No. 2009-014889, Ms. Rin-Laures.

JUDGE SPIEGEL: We're here for oral arguments in Appeal No. 2009-014889, in the matter of ex parte Brockhaus, Application No. 08/444790. If counsel will kindly introduce herself and her guests, you may proceed when ready. You have 20 minutes for argument.

MS. RIN-LAURES: I have here a visual aide.

JUDGE SPIEGEL: Visual aids will not be admitted into the record at this point.

MS. RIN-LAURES: It's from the record.

JUDGE SPIEGEL: I'm saying it will not be entered into the record. After the argument, you take them back.

MS. RIN-LAURES: Okay.

JUDGE SPIEGEL: The reason being the Examiner has not had a chance to comment on this, therefore, it will not become part of the record.

MS. RIN-LAURES: Okay.

May it please the Court, my name is Lily Rin-Laures, representing the Appellant; and I have with me here today, Kathleen Fowler and Rosemary Sweeney, also representing Appellant.

The Appellant's invention is the combination of two known components that together function in a way that the Examiner admits is unexpected. We're here today because the Examiner is trying to limit Appellants to less than they actually possessed and described as their invention.

I've provided you with a visual aide that contains figures from the Appeal Brief. The pages are noted on the visual aide. You can see that the invention is a combination of two components.

The invention as depicted in Box C and Box A is one component. It is all of the domains of a heavy chain constant region other than the first domain of an immunoglobulin. So that's the CH3, CH2, and hinge domain.

Box B is the second component of the claimed invention, and that is the TNF binding soluble fragment of a TNF receptor.

You put them together, you get Box C, which is the claimed invention.

The two main rejections at issue are written description and obviousness.

The written description rejection should be reversed because the Examiner first erred by limiting the invention to a partial sequence displayed in Figure 4, when the Examiner admits that the inventor purified, sequenced and possessed the entire receptor.

Second, the Examiner disregarded unrebutted, declaratory testimony from Dr. Lyman that one of skill in the art understood that the description conveyed using the entire extra-cellular domain or fragments.

Third, the Examiner misapplied controlling federal circuit case law because he approached the invention as a discovery of a novel gene. It's not. The invention is a combination of known sequences that when put together each function in a way that was different from what had been predicted.

The obviousness rejection should be reversed for two major reasons. The first is that the Examiner disregarded overwhelming evidence of six different kinds of admittedly unexpected results because of the supposed lack of written description. And the Examiner failed to articulate a logical reason

why one of ordinary skill in the art would have combined these two components, which have admittedly opposite effects.

The Examiner agrees that the TNF receptor portion of the fusion protein is anti-inflammatory, and the immunoglobulin portion of the fusion protein is pro-inflammatory because it has a effector functions that are responsible for killing cells and lysine cells.

So since the case was Briefed to the Board, we've had the benefit of the federal circuit's En Banc decision and Ariad v. Lilly, which has told us that the purpose of the written description requirement is to insure that Applicants don't claim more than what they've invented.

So turning to the application, what did the inventors invent? The application describes the invention -- remember, it has to be read from the viewpoint of the skilled artisan with the knowledge in the art as of the effective filing date, August 31, 1990.

If you look at the working examples, you can see that the inventors were concerned with finding --

JUDGE SPIEGEL: Excuse me. There's no debate as to what the effective filing date is in this line of CIDs?

MS. RIN-LAURES: That's correct. That's not disputed.

JUDGE SPIEGEL: Thank you.

MS. RIN-LAURES: You can see the focus of their research was TNF receptors. They purified two different TNF receptors, 55 kilodalton and 75 kilodalton. They sequenced them. They had their end terminus as well as the internal peptides. They used those sequences to clone CDNA in coding both of the receptors, and you can see that in Figure 1 there's the complete

sequence for the P55 receptor and in Figure 4 there's a partial, but almost complete sequence, for the 75 kilodalton receptor. It's missing the first 48 amino acids of approximately 400 amino acid proteins.

Then the application provides you with the citation to a reference that contains the complete published sequence of the 75 kilodalton receptors. That's at page 10, line 10, of the Smith Science Article, 1990.

The application describes cutting out TNF binding soluble portions of the complete -- it uses the word complete -- receptor sequence, using known methods, at page 14. Example 11 describes a working example of a P55 complete extra-cellular domain used to hinge CH2 and CH3 regions of an immunoglobulin. So this is all that it provides in terms of working examples.

Then, if you look at the description, what are they trying to claim? What have they invented? The summary of invention is very short. It says they're concerned with TNF receptors; and, in particular, they're concerned with a fusion protein that contains soluble TNF binding fragments fused to all of the domains of the constant region of the heavy chain of an immunoglobulin, other than the first domain.

So that's exactly what we're claiming now, and that's what was in original Claim 17 of the application as well.

JUDGE MILLS: Aren't you claiming those 75 kilodalton proteins in Claim 62?

MS. RIN-LAURES: Yes.

JUDGE MILLS: Okay.

MS. RIN-LAURES: I'm sorry, the particular TNF receptor -- you're correct

-- that we're claiming is the human 75 kilodalton receptor that we've identified in Claim 62 by its molecule weight and by the 18 amino acids of its end terminal sequence, which the Examiner agrees uniquely identifies that particular protein.

So what does this mean to one of ordinary skill in the art? We provided declaratory testimony from Dr. Lymon saying when you see the term soluble fragment the skilled artisan understands that to mean the extra cellular domain of a receptor or fragment of that receptor.

The Examiner actually agrees at page 24 of the answer that this is -- sorry, page 34 -- that this is consistent with the usage in the art and how the skilled artisan would understand the term soluble fragment.

If you look at the application again, you'll see that the application talks about, again, taking soluble portions of the TNF receptors and using known methods to make fragments, and testing them for activity using an assay that we provided in Example 1. All of these things are easily done and well within the skill of the art.

We cited two cases, federal circuit cases in our Appeal Brief: Capon v. Eshhar and Faulkner v. Inglis that also dealt with inventions that were novel combinations or novel uses of known sequences.

If you'll compare the scope of our claims to the scope of those claims, our's are much, much narrower. So Capon, for example, is any antibody-binding domain fused to any intracellular portion of the receptor.

In Faulkner v. Inglis, it was any inactivating mutation and any essential pox virus gene, when the application didn't have any sequences of any pox virus genes at all.

So in contrast, our claims are to a specific protein fused to a very specific confirmation of an immunoglobulin fragment: the hinge, CH2 and CH3. Our claims are much narrower.

So for all of these reasons, the Examiner should be reversed on the written description rejection because the Examiner is trying to limit the Appellant to less than what they actually posses, and less than they described in the application.

The full scope of what they describe is a soluble fragment of the TNF receptor fused to this portion of the immunoglobulin.

Are there any questions on written description?

JUDGE SPIEGEL: Keep going.

MS. RIN-LAURES: Or what the position is? Okay.

On the obviousness rejection, the Examiner agreed that the Applicant had provided six different kinds of unexpected results. These results were unexpected, pages 63 to 65.

The Examiner also admits that the tested embodiments are within the scope of the claims at page 62. So the refusal to substantively consider these unexpected results is reversible error.

You can see from the results that each component of this invention is functioning differently. The immunoglobulin portion of the fusion protein, which has effector functions and which is expected to retain those effector functions, lacks them. They're completely out of synch, or markedly reduced both ADCC and CDC, so that's functioning differently.

The TNF binding portion of the fusion protein is also functioning differently than one would have predicted. Compare to the monomeric form of just the

soluble fragment, the fusion protein, when you combine it with the immunoglobulin, hinge CH2 and CH3, binds TNF more tightly.

You can see that with its increased binding affinity, its slower disassociation kinetics, as well as a very surprising thousand-fold increase in TNF neutralizing potency that wouldn't have been predicted from the fifty-fold increase in binding affinity.

In combination, these elements have a different binding geometry, which you can see from the sixth unexpected result which is that it does not aggregate when it binds TNF.

JUDGE MILLS: The unexpected results were delineated in the first Lyman declaration, is that correct?

MS. RIN-LAURES: The unexpected results are discussed in the Appeal Brief, and they draw on data provided in the Lesslauer declaration.

JUDGE MILLS: Oh, Lesslauer, okay.

MS. RIN-LAURES: Which talks about the slower disassociation kinetics and better binding affinity. The Mohler reference, which talks about the fifty-fold increase binding affinity, the thousand-fold increased potency. The Barone abstract, the Khare poster and the Kohno poster, which are all in the record as well, contain the evidence that these two components when together don't aggregate, don't have ADCC and don't have CDC, which are the immunoglobulin effector functions.

Do you need citations to the record for those?

JUDGE MILLS: No, that's okay.

So what was the Examiner's position with regard to the obviousness rejection? I think we were relying on an embodiment where the antibody

was used in the assay.
MS. RIN-LAURES: Yes, so because of his mistaken position on written description saying that the only thing that the Applicant invented was a fragment of Figure 4, which was characterized as a partial sequence, the Examiner took the position that the tested embodiments, which he admitted fell within the scope of the claim, didn't need to be considered because they were the entire extra cellular domain rather than a fragment of Figure 4.
So you can see that the obviousness rejection is all wrapped up in a written description rejection, which is not appropriate.
You look at what's claimed. You look at the unexpected results for what's claimed, and that renders the application obvious.
The other part of the obviousness rejection was the rationale for combining the two elements together, and there was not a logical, scientific reason for doing that.
JUDGE SPIEGEL: Was there not a reason, or was there simply a different reason from that which your application sets forth?
MS. RIN-LAURES: Well, the original reason that we argued was that there was no reason to combine an anti-inflammatory with a pro-inflammatory component.
JUDGE SPIEGEL: My question was, was the reason that the Examiner gave for the combination simply different from the reason that the combination was made in your application?
MS. RIN-LAURES: Yes.
JUDGE SPIEGEL: And -- second part -- given that it was a different reason, where in the record did you substantively argue that the Examiner's

proffered reason was inoperable for the reason given by the Examiner?
MS. RIN-LAURES: In the Reply Brief we responded to the Examiner's rationale which moved to an invitro reason for combining the two for the purposes of affinity-purifying TNF. But when you examine that rationale, it doesn't point you to a particular embodiment that makes it --
JUDGE SPIEGEL: However, the Examiner's rationale is both reasonable and believable on its face.
MS. RIN-LAURES: No, I disagree.
JUDGE SPIEGEL: You disagree?
MS. RIN-LAURES: I disagree.
JUDGE SPIEGEL: You disagree that this compound cannot be used for affinity purification of TNF soluble ligand?
MS. RIN-LAURES: I disagree that the rationale provides you with a reason for choosing the particular confirmation of the immunoglobulin which has not only CH3 but also CH2 and hinge.
So the only part of the fusion protein that you really need for affinity purification is the TNF receptor part. That's the part that binds TNF.
Logically, if you are going to fuse -- you don't really need to fuse anything to it, but if you were going to fuse something to it, you would fuse the least possible so as to avoid any complications.
So if you were going to --
JUDGE SPIEGEL: However, the Examiner's proffer is not inoperable for the utility of ligand purification -- yes or no? It may not be the best. That's not the question.
The question is: is it inoperative or not for ligand purification?

MS. RIN-LAURES: Well, I think the question is would you have selected --
JUDGE SPIEGEL: The question from the bench is, is it operative or not for ligand purification?
MS. RIN-LAURES: I suspect it would be operative for ligand purification.
JUDGE SPIEGEL: Thank you.
MS. RIN-LAURES: But I do not think --
JUDGE SPIEGEL: Thank you.
MS. RIN-LAURES: I do not think that's the embodiment that's actually motivated by the specific rationale.
JUDGE SPIEGEL: Secondly, the Examiner's position on unexpected results appears to be that your showing is not commensurate in scope with the claimed invention.
MS. RIN-LAURES: That is not the position that was taken in the Examiner's answer.
JUDGE SPIEGEL: Can you point me to where that is not?
MS. RIN-LAURES: The first paragraph of the Examiner's answer says that that was deleted from the answer in response to a petition.
The Examiner has provided no evidence or reasoning as to why the unexpected results would not be representative of the scope of the relatively narrow claims. So we're not claiming analogs. The application discusses analogs, but that is not in the claim language.
We're claiming soluble fragments --
THE COURT: Excuse me, first page, first paragraph of the Examiner's answer reads:
"This is in response to the Appeal Brief filed 28th of February, 2008

(02/28/2008) appealing from the office action mailed 23 February, 2007 (02/23/2007). This replaces the Examiner's answer mailed on 14 August, 2008 (8/14/2008) and 26 February, 2009 (2/26/2009) in view of the 9/23/2008 decision for the petition filed on 28 August, 2008 (8/28/2008) and on reconsideration it is decided that the first petition was fully persuasive; and, therefore, this new answer is being sent which omits reference to the potential new rejection which was originally denied."

You're saying the revised Examiner's answer mailed on 2/26/2009 inadvertently retained material included in the grounds of petition? You're saying that is the reference which says the Examiner has withdrawn his position that the showing of unexpected results is not commensurate in scope with the claimed invention?

MS. RIN-LAURES: Yes, that was deleted from the Examiner's answer. But, in any case, there is no specific evidence or reasoning that would lead one to believe that at least one of the six different kinds of unexpected results wouldn't apply across the scope of the claim.

Again, it's not a broad claim. It's the extracellular domain, or fragments thereof, that retain TNF binding activity. So we've already limited the claim to those embodiments that have TNF binding activity and who require the fusion protein have TNF binding activity as well.

The invention is the combination of the TNF binding fragment with the hinge CH2 and CH3 domain of the immunoglobulin. So as long as you retain the TNF binding activity, one would expect these unexpected results to be observed.

Biological micromolecules are forgiving of a little bit of addition here, a

little bit of addition there. You can see we did provide in the record evidence that after the publication date others had made fragments of the TNF extracellular domain of the P75 TNF receptor, and had shown that you could truncate to 162 and it would retain TNF binding activity. But if you went further than that, you would destroy TNF binding activity.

So I did want to revisit the point you made earlier --

JUDGE SPIEGEL: If you truncate that far down, then you don't have an apparent molecular weight of about 75 KDA on the non-reducing SDS gel, do you?

MS. RIN-LAURES: That's correct.

JUDGE SPIEGEL: Okay.

MS. RIN-LAURES: The 75 kilodalton refers to the full length receptor. So remember there were two purified in the application. One was 55 kilodaltons and one was 75 kilodaltons. That's the identification of which the full length receptors from which a soluble fragment is being claimed.

JUDGE SPIEGEL: So the fragment being used can be much lower than 75 KDA?

MS. RIN-LAURES: That's correct.

JUDGE SPIEGEL: As long as it has the amino acid sequence of ID Number 10 included.

MS. RIN-LAURES: That's correct. Because sequence ID Number 10 is the first 18 amino acids, and that is sufficient to identify which protein is being used for the soluble fragment portion of it.

In addition, we did separately argue a claim in which the amino terminus is limited to including SEQ ID 10. So you can't trim from both ends. You can

only trim from the C terminal end, if that makes sense.

JUDGE SPIEGEL: Okay.

MS. RIN-LAURES: I did want to readdress your previous question with respect to the embodiment that is motivated by the Examiner's rationale for affinity purification.

There's a couple of things that you need to remember. Capon describes hundreds of different embodiments, and if one were to follow the Examiner's rationale, one would be led away from the dimeric form of the fusion protein.

Why make things more complicated than they have to be? All you need is a TNF receptor binding portion. There's no need to fuse any extra bits of the immunoglobulin to it.

The second thing I wanted to bring to your attention was that we have separately argued claims that are directed to pharmaceutical compositions of the fusion protein. Those are sterile because you're delivering a protein.

The Examiner's invitro-affinity purification rationale does not extend to making sterile compositions, which would be suitable for treating illness in which TNF is involved.

JUDGE SPIEGEL: I don't have any questions. Thank you very much for stating your position. We thank you all for coming, and the case is taken under advisement.

MS. RIN-LAURES: Thank you.

(Whereupon, the proceedings at 9:28 a.m. were concluded.)